Ensemble response of immune repertoires to vaccination

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Short Abstract — **The T-cell repertoire response to the yellow fever vaccine builds near total immunity. To quantify the response we developed a statistical model of differential T-cell proliferation and used it as a basis for inference from high-throughput receptor sequencing data obtained from individuals pre and post vaccination. While the learned model for replicate statistics varies little across time points, the repertoire ensemble parameters vary, consistent with YF response timescales. Finally, we identify candidate clones responsive to the vaccine by their posterior expansion probability. These candidates are experimentally validated.**

Keywords **— Immune repertoire, inference, vaccine response.**

I. Background

THE efficacy of a vaccine depends strongly on its interactions with the immune repertoire: a vast set of receptors capable of focusing immune defenses on infectious agents. These interactions leave signatures in the sequences and relative frequencies of immune clones. High throughput sequencing now provides measurements of millions of receptors, allowing for characterizing the repertoire at the level of the ensemble [1]. In spite of large scale efforts [2], how repertoire statistics respond to infection is unknown. This limits our ability to predict which TCR sequence will respond to a given antigen. The attenuated yellow fever (YF) vaccine induces near total immunity in humans and serves as human model for acute viral infection [3]. We developed a methodology for identifying responding clonotypes from time-dependent repertoire-sequencing data and applied it to sequencing measurements before and after YF vaccination.

II. Methods

We developed accurate models of the variation in sampled receptors molecules between a pair of replicates. We then assessed functional forms for a prior on the log fold-change of clone frequency via the likelihood-based criterions of the corresponding observed marginal distribution of pair counts. We combined these to obtain a model of differential expression. Inverting this model gave the posterior log fold-change probability of a clone given an observed count pair. The latter served to make inferences about the response of individual clones. Finally, we ran an experimental validation assay and compared these to those identified by our method.

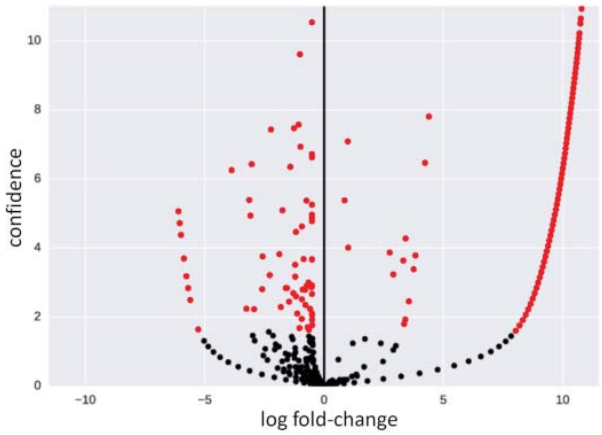

Fig. 1. Confidence of clone contraction (left) and expansion (right) as a function of fold-change of the hidden clone frequency. Circles denote pairs of measured cell counts. Red circles denote clones significantly affected by vaccination.

III. Results

A two-step replicate model best fit our data, giving similar parameter values across days, suggesting a unique natural replicate statistics. By combining this model with the best fitting log fold-change prior, we found correlated variation in the learned prior parameters values that systematically varied in time after vaccination. For each time point, the list of significantly expanded clones (see Fig. 1) correlated highly to the results of our experimental validation assay.

IV. Conclusions

Inferred changes in ensemble parameters of repertoire statistics reflect repertoire-level response dynamics. They are consistent with the known time scales of the response to YF and suggest temporally-sensitive ensemble features subject to homeostatic constraints. Finally, our validated method can detect significantly expanded clones by accounting for the natural variation in clone statistics.

References

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Acknowledgements: This work was funded by ERCCoG grant no. 724208.

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